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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/807,897	03/24/2004	Rong Xiang	TSRI 874.1	6550

7590 12/13/2006

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/807,897	XIANG ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 16-53* is/are pending in the application.

4a) Of the above claim(s) *3-9, 16-25, 30-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,26-29 and 51-53* is/are rejected.

7)☒ Claim(s) *26 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/807,897 filed on March 24, 2004 claims the benefit of 60/457,009 filed on 03/24/2003.

Election/Restriction

1. Applicant's election without traverse of Group VII, Claims 1, 26 (each in part), 27-29, drawn to a DNA vaccine suitable for eliciting an immune response against cancer comprising a DNA construct operably encoding at least one cancer-associated Inhibitor of Apoptosis-family protein (IAP-family) protein, encoded by polynucleotide sequences of SEQ ID No: 3, and at least one immunoactive gene product in a pharmaceutically acceptable carrier in the reply filed on Nov. 6, 2006 is acknowledged.

It is noted that applicants amended claim 2 and added new claims 51-53, and the amended claim 2 and newly added claims 51-53 are now assigned to Group VII.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3-9, 16-25, 30-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. In the amended claims filed on November 6, 2006, applicant cancelled claims 10-15.

Status of claims: Claims 1, 2, 26-29, and 51-53 are currently under examination.

Claim Objections

2. Claims 26 and 28 are objected to because of the following informalities: recitations of non-elected SEQ ID NOs. Appropriate correction is required.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 2, 26-29, and 51-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one cancer-associated Inhibitor of Apoptosis-family protein (IAP-family protein) and at least one immunoactive gene product in a pharmaceutically acceptable carrier (claim 1).

With regard to IAP-family protein, the specification stated, (i) "the term "IAP-family protein" as used herein and in the appended claims includes any of the class of natural antigens expressed in tumor cells, which inhibit apoptosis in their natural form", and (ii) "the term " IAP-

family protein" as used herein and in the appended claims also includes variants of wild-type IAP proteins such as splice variants and substitution variants, and the like, as well as fragments and immunogenic homologs thereof that bind to a major histocompatibility (MHC) class I molecule and are recognized by cytotoxic T-cells (i.e., survivin protein epitopes)" (See paragraph [1190]).

With regard to immunoactive gene product, the specification stated, (i) immunoactive gene products encoded by the DNA constructs of the present vaccines are preferably cytokines or ligands of natural killer cell surface receptors. (See paragraph [0135]), and (ii) due to the inherent degeneracy of the genetic code, DNA sequences that encode substantially the same or a functionally equivalent amino acid residue sequence to the useful native immunoactive gene products (See paragraph [0148]).

Based upon the prior art and specification disclosed in the instant application, there is expected to be variation among the species of cDNA, which encode either IAP family proteins or immunoactive gene products. In the absence of a functional assay it would not be possible to test variants of the claimed DNA vaccine for biological activity. Also with regard to the claimed allelic variants, the skilled artisan cannot envision the structure of such a variant because such variants are randomly produced in nature, and cannot be predicted from a known sequence. The specification does not teach any characteristics of an "allelic" variant that would distinguish it from a non-natural variant constructed by the hand of man.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because a murine survivin and a murine CCL21 cDNA sequence are not

representative of the claimed genus of a IAP-family protein and a immunoactive product. Consequently, applicant was in possession of only the polynucleotide encoding murine survivin cDNA (SEQ ID NO: 3), and polynucleotide encoding murine CCL21 cDNA (SEQ ID NO: 7), and. In conclusion, applicant was not in possession of the genus of IAP-family protein and immunoactive gene product as encompassed by the claims. In agreement with this conclusion, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that, "the inventor invented the claimed invention."

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 2, 26, and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al. (Bennett et al. U.S. Patent No. 6,335,194 and WO200157059-A1)

Bennett et al teach antisense modulation of survivin expression, compositions and methods are provided for modulating the expression of survivin, and methods of using antisense compounds for modulation of survivin expression and for treatment of diseases associated with expression of survivin (See title and abstract, Bennett et al.).

With regard to SEQ ID NO: 3, which encodes a murine surviving, Bennett et al. teach DNA encoding mouse survivin that matches perfectly with SEQ ID NO: 3 (See Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55, detailed alignment of sequences listed below).

With regard to immunoactive gene product, Bennett et al. teach expression vector containing coding sequence of surviving (See column 1, third paragraph). The expression vector contains DNA sequences encoding selection marker for transfection and/or a reporter gene for detection. It is noted that the gene product (for instance, *LacZ*) from the expression vector would be immunoactive because it is foreign to the immune system. This is evident and supported by Ambrosini et al. (Ambrosini et al., Induction of apoptosis and inhibition of cell proliferation by survivin gene targeting. *J Biol Chem.* 273(18): 11177-82, 1998; cited by Bennett et al.).

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RESULT 1
AAS21530
ID   AAS21530 standard; cDNA; 955 BP.
XX
AC   AAS21530;
XX
DT   21-NOV-2001  (first entry)
XX
DE   DNA encoding mouse survivin.
XX
KW   Survivin; human; mouse; cytostatic; antisense oligonucleotide;
KW   hyperproliferative condition; cancer; apoptosis; cytokinesis; ss.
XX
OS   Mus musculus.
XX
PN   WO200157059-A1.
XX
PD   09-AUG-2001.
XX
PF   30-JAN-2001; 2001WO-US002939.
XX
PR   02-FEB-2000; 2000US-00496694.
XX
PA   (ISIS-) ISIS PHARM INC.
XX
PI   Bennett CF,  Ackermann EJ,  Swayze EE,  Cowsert LM;
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XX
DR WPI; 2001-488863/53.
XX
PT Novel antisense compounds for modulating the expression of Survivin and
PT treatment of cancer.
XX
PS Example 13; Page 80-81; 120pp; English.
XX
CC The invention relates to antisense oligonucleotides targeted to a nucleic
CC acid molecule encoding human Survivin, where the antisense
CC oligonucleotide inhibits the expression of human Survivin. These
CC antisense oligonucleotides are used in the treatment of an animal
CC suffering from a disease or condition associated with Survivin, e.g. a
CC hyperproliferative condition such as cancer, and comprises administering
CC a therapeutically or prophylactically effective amount of the antisense
CC oligonucleotide so that expression of Survivin is inhibited. The
CC oligonucleotides can also be used to treat a human suffering from a
CC disease or condition characterised by a reduction in apoptosis comprising
CC administering the antisense oligonucleotide to a human. In addition, the
CC antisense oligonucleotide and a cytotoxic chemotherapeutic agent e.g.
CC taxol or cisplatin, can be used to modulate apoptosis, cytokinesis or the
CC cell cycle, or inhibit the proliferation in a cancer cell by contacting
CC the cell with the antisense oligonucleotide. AAS21521-AAS21768 represent
CC Survivin nucleic acids, and antisense oligonucleotides targeted to
CC Survivin, used in the method of the invention
XX
SQ Sequence 955 BP; 230 A; 227 C; 265 G; 233 T; 0 U; 0 Other;

Query Match 100.0%; Score 955; DB 5; Length 955;
Best Local Similarity 100.0%; Pred. No. 3.6e-284;
Matches 955; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 GGCACGAGGGGGCCGGGGCTCTCCCGGCATGCTCTGCGGCGCGCCTCCGCCCGCGCGATT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GGCACGAGGGGGCCGGGGCTCTCCCGGCATGCTCTGCGGCGCGCCTCCGCCCGCGCGATT 60

Qy         61 TGAATCCTGCGTTTGAGTCGTCTTGGCGGAGGTTGTGGTGACGCCATCATGGGAGCTCCG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TGAATCCTGCGTTTGAGTCGTCTTGGCGGAGGTTGTGGTGACGCCATCATGGGAGCTCCG 120

Qy        121 GCGCTGCCCCAGATCTGGCAGCTGTACCTCAAGAACTACCGCATCGCCACCTTCAAGAAC 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GCGCTGCCCCAGATCTGGCAGCTGTACCTCAAGAACTACCGCATCGCCACCTTCAAGAAC 180

Qy        181 TGGCCCTTCCTGGAGGACTGCGCCTGCACCCCAGAGCGAATGGCGGAGGCTGGCTTCATC 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 TGGCCCTTCCTGGAGGACTGCGCCTGCACCCCAGAGCGAATGGCGGAGGCTGGCTTCATC 240

Qy        241 CACTGCCCTACCGAGAACGAGCCTGATTTGGCCCAGTGTTTTTTCTGCTTTAAGGAATTG 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 CACTGCCCTACCGAGAACGAGCCTGATTTGGCCCAGTGTTTTTTCTGCTTTAAGGAATTG 300

Qy        301 GAAGGCTGGGAACCCGATGACAACCCGATAGAGGAGCATAGAAAGCACTCCCCTGGCTGC 360
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                    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 GAAGGCTGGGAACCCGATGACAACCCGATAGAGGAGCATAGAAAGCACTCCCCTGGCTGC 360

Qy        361 GCCTTCCTCACTGTCAAGAAGCAGATGGAAGAACTAACCGTCAGTGAATTCTTGAAACTG 420
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 GCCTTCCTCACTGTCAAGAAGCAGATGGAAGAACTAACCGTCAGTGAATTCTTGAAACTG 420

Qy        421 GACAGACAGAGAGCCAAGAACAAAATTGCAAAGGAGACCAACAACAAGCAAAAAGAGTTT 480
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 GACAGACAGAGAGCCAAGAACAAAATTGCAAAGGAGACCAACAACAAGCAAAAAGAGTTT 480

Qy        481 GAAGAGACTGCAAAGACTACCCGTCAGTCAATTGAGCAGCTGGCTGCCTAATGCTGAGCC 540
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 GAAGAGACTGCAAAGACTACCCGTCAGTCAATTGAGCAGCTGGCTGCCTAATGCTGAGCC 540

Qy        541 TTTGCTGAGATAACTTGGACCTGAGTGACATGCCACATCTAAGCCACGCATCCCAGCTTT 600
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 TTTGCTGAGATAACTTGGACCTGAGTGACATGCCACATCTAAGCCACGCATCCCAGCTTT 600

Qy        601 TCCAGCCAGGGCCTCCTAGCAGGATCTTAGAGAAGGAGACAGTGGTATTTTGAAACTGGA 660
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 TCCAGCCAGGGCCTCCTAGCAGGATCTTAGAGAAGGAGACAGTGGTATTTTGAAACTGGA 660

Qy        661 TATCAAATATTTTTGGTTTTGCTTTAAAGTGGCTACCTCTCTTTGGTTTTGTGGCTTTGC 720
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 TATCAAATATTTTTGGTTTTGCTTTAAAGTGGCTACCTCTCTTTGGTTTTGTGGCTTTGC 720

Qy        721 TCTATTGTGACGTGGACTTAAGCAATAAGGAAGTGATGAAGGGACAGTGTTCTCTGACAG 780
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 TCTATTGTGACGTGGACTTAAGCAATAAGGAAGTGATGAAGGGACAGTGTTCTCTGACAG 780

Qy        781 GACCTGTGGGGGTCGGGGTGCCTGTGCAAGGTCTTGGTTCTGATTGTGATATTTCCATAC 840
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        781 GACCTGTGGGGGTCGGGGTGCCTGTGCAAGGTCTTGGTTCTGATTGTGATATTTCCATAC 840

Qy        841 AGGGCTGCTAATGCAGCCCATGGGTAAGTGTGGTTATATGTGTTTGTGCTGATAATTTTG 900
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 AGGGCTGCTAATGCAGCCCATGGGTAAGTGTGGTTATATGTGTTTGTGCTGATAATTTTG 900

Qy        901 TCCTGATGAGTTTTCCTACCACGGGGTAACGGAATAAAATCACTTGAAAAAGTGG 955
                    |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 TCCTGATGAGTTTTCCTACCACGGGGTAACGGAATAAAATCACTTGAAAAAGTGG 955
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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-2 and 51-53 are rejected under 35 U.S.C. 102(e) as being anticipated by Girard et al. (US patent publication No. 2004/0224408, publication date Nov. 11, 2004).

It is noted that the claims language "a polynucleotide sequences represented by SEQ ID NO: 3 (or 7)" in claims 51-53 are interpreted as "polynucleotide sequences encoding homologous genes to the gene encoded by SEQ ID NO: 3 (or 7)". Thereby, the breadth of the claims would read on (i) any polynucleotide sequences encoding mammalian survivin (as SEQ ID NO: 3 encodes murine survivin), and (ii) any polynucleotide sequences encoding mammalian chemokine CCL21 (as SEQ ID NO: 7 encodes murine CCL21).

Girard et al. teach genes and proteins of the THAP family comprising a THAP domain, and their use in diagnostics, treatment of disease, and in the identification of molecules for the treatment of disease. Girard et al. also teach the uses of THAP-type chemokine-binding agents, such as THAP-family proteins, as nuclear receptors for a chemokines and to methods for the modulation (stimulation or inhibition) of transcription, cell proliferation and cell differentiation as well as methods for identifying for compounds that modulate THAP chemokine interactions (See, title and abstract).

With regard to survivin, a cancer-associated inhibitor of Apoptosis-family protein (claims 1-2, and 51-53 of instant application), Girard et al. teach that, survivin has been shown to be a

critical anti-apoptotic factor at the interface between cell cycle/mitosis and apoptosis. Down regulation of surviving expression by THAP1 may therefore contribute to its pro-apoptotic activity (see Example 10). Simultaneous down-regulation by THAP1 of all these genes critical for cell cycle/cell proliferation and/or apoptosis (CKS1, *Survivin*, PTTG1/Securin, MAD2L1, USP16, HMMR) is expected to result in cell cycle block and inhibition of cell proliferation. (See paragraph [1459], Girard et al. US patent publication No. 2004/0224408, publication date Nov. 11, 2004).

Girard et al. further teach role in mitosis/chromosome segregation: Survivin (polypeptide sequence SEQ ID NO: 343, nucleotide sequence SEQ ID NO: 344) (Li et al. (1998) *Nature* 396:580-584; Li et al. (1999) *Nature Cell Biol* 1:461-466; Lens et al. (2003) *EMBO J* 22:2934-2947)" (See Fig. 30,Table 2A, 2B, paragraph [1454], Girard et al.). It is noted that Lens et al. (2003) *EMBO J* 22:2934-2947, cited by Girard et al., teach mouse survivin and the phenotype of the survivin-deficient mice partially overlaps with that observed in mouse embryos deficient for INCENP.

With regard to polynucleotide encodes an immunoactive gene product, chemokine CCL21 (claims 1-2 and 51-53 of instant application), Girard et al. teach that human SLC/CCL21 cDNA encodes a 134 amino acid residue, highly basic, precursor protein with a 23 amino acid residue signal peptide that is cleaved to form the predicted 111 amino acid residues mature protein. Mouse SLC/CCL21 cDNA encodes a 133 amino acid residue protein with 23-residue signal peptide that is cleaved to generate the 110 residue mature protein. Human and mouse SLC/CCL21 is highly conserved, exhibiting 86% amino acid sequence identity (See paragraph [0014]).

With regard to immune response (claims 1-2, and 51-53 of instant application), Girard et al. teach "some chemokines act selectively on immune system cells such as subsets of T-cells or B lymphocytes or antigen presenting cells, and may thereby promote immune responses to antigens" (See paragraph [0012]).

With regard to vaccine and pharmaceutical composition, Girard et al. teach "some embodiments of the present invention relate to a device for delivering the THAP-type chemokine-binding agent or pharmaceutical composition thereof to the subject. In such embodiment, the device comprises a container that contains the THAP-type chemokine-binding agent or pharmaceutical composition thereof. For example, in some embodiments, the device may be a conventional device including, but not limited to, syringes, devices for intranasal administration of compositions and vaccine guns (See paragraph [1247]).

With regard to DNA construct for expression of proteins, Girard et al teach plasmids and other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions (See paragraph [0986]).

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 26, 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. (Bennett et al. U.S. Patent No. 6,335,194 and WO200157059-A1) taken with Pawelek et al. (U.S. patent 6,190,657, date of patent Feb. 20, 2001).

Bennett et al teach antisense modulation of survivin expression, compositions and methods are provided for modulating the expression of survivin, and methods of using antisense compounds for modulation of survivin expression and for treatment of diseases associated with expression of survivin (See title and abstract, Bennett et al.).

With regard to SEQ ID NO: 3, which encodes a murine surviving, Bennett et al. teach DNA encoding mouse survivin that matches perfectly with SEQ ID NO: 3 (See Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55, detailed alignment of sequences listed below).

With regard to immunoactive gene product, Bennett et al. teach expression vector containing coding sequence of surviving (See column 1, third paragraph). The expression vector contains DNA sequences encoding selection marker for transfection and/or a reporter gene for detection. It is noted that the gene product (for instance, *LacZ*) from the expression vector would be immunoactive because it is foreign to the immune system. This is evident and supported by Ambrosini et al. (Ambrosini et al., Induction of apoptosis and inhibition of cell proliferation by survivin gene targeting. *J Biol Chem.* 273(18): 11177-82, 1998; cited by Bennett et al.).

However, Bennett et al. do not teach attenuated strains of *Salmonella typhimurium* as vectors for delivery of DNA construct.

At the time the claimed invention was made, attenuated strains of *Salmonella typhimurium* as vectors for delivery of DNA construct is known in the art. For instance, Pawelek et al. (U.S. patent 6,190,657, date of patent Feb. 20, 2001) teach the isolation and use of super-infective, tumor-specific, attenuated strains of parasites including, but not limited to, bacteria, fungi and parasites. In certain embodiments the parasites include the bacterium *Salmonella* spp., such as *Salmonella typhimurium*, the bacterium *Mycobacterium avium*, and the protozoan *Leishmania amazonensis*, for the diagnosis and treatment of sarcomas, carcinomas, and other solid tumor cancers. In other embodiments, the present invention is concerned with the isolation and use of super-infective, tumor-specific, suicide gene-containing strains of parasites (See Filed of Invention, column 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to modify the delivery of DNA construct by expression vectors taught by Bennett et al. and replaced with attenuated strains of *Salmonella typhimurium* harboring the expression vectors as vectors for delivery of DNA construct, by the teachings of Pawelek et al., in order to achieve the goal of obtaining strong, specific, and long lasting immune responses after expression of DNA construct bearing coding sequences of survivin and an immunoactive gene product in the vaccinated individual.

One having ordinary skill in the art would have been motivated to replace expression vectors with attenuated strains of *Salmonella typhimurium* vectors because the attenuated strains of *Salmonella typhimurium* vectors are super-infective and tumor-specific, and feasible for oral infection to vaccinate an individual.

There would have been a reasonable expectation of success given (i) delivery of DNA construct with expression vectors by the teachings of Bennett et al., and (ii) the attenuated strains of *Salmonella typhimurium* vectors being super-infective and tumor-specific in the treatment of solid tumor, including melanoma, by the teachings of Pawelek et al. for a skilled person in the art to employ *Salmonella typhimurium* vectors to deliver a DNA construct expressing survivin and an immunoactive gene product, giving rise to specific and protective immune responses after delivery of the DNA vaccine in an individual.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

7. Claims 1, 28, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Girard et al. (US patent publication No. 2004/0224408, publication date Nov. 11, 2004) taken with Tanabe et al. (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997).

It is noted that the claims language "a polynucleotide sequences represented by SEQ ID NO: 3 (or 7)" in claims 51-53 are interpreted as "polynucleotide sequences encoding homologous genes to the gene encoded by SEQ ID NO: 3 (or 7)". Thereby, the breadth of the claims would read on (i) any polynucleotide sequences encoding mammalian survivin (as SEQ ID NO: 3 encodes murine survivin), and (ii) any polynucleotide sequences encoding mammalian chemokine CCL21 (as SEQ ID NO: 7 encodes murine CCL21).

Girard et al. teach genes and proteins of the THAP family comprising a THAP domain, and their use in diagnostics, treatment of disease, and in the identification of molecules for the

treatment of disease. Girard et al. also teach the uses of THAP-type chemokine-binding agents, such as THAP-family proteins, as nuclear receptors for a chemokines and to methods for the modulation (stimulation or inhibition) of transcription, cell proliferation and cell differentiation as well as methods for identifying for compounds that modulate THAP chemokine interactions (See, title and abstract).

With regard to survivin, a cancer-associated inhibitor of Apoptosis-family protein (claims 1-2, and 51-53 of instant application), Girard et al. teach that, survivin has been shown to be a critical anti-apoptotic factor at the interface between cell cycle/mitosis and apoptosis. Down regulation of surviving expression by THAP1 may therefore contribute to its pro-apoptotic activity (see Example 10). Simultaneous down-regulation by THAP1 of all these genes critical for cell cycle/cell proliferation and/or apoptosis (CKS1, *Survivin*, PTTG1/Securin, MAD2L1, USP16, HMMR) is expected to result in cell cycle block and inhibition of cell proliferation. (See paragraph [1459], Girard et al. US patent publication No. 2004/0224408, publication date Nov. 11, 2004).

Girard et al. further teach role in mitosis/chromosome segregation: Survivin (polypeptide sequence SEQ ID NO: 343, nucleotide sequence SEQ ID NO: 344) (Li et al. (1998) *Nature* 396:580-584; Li et al. (1999) *Nature Cell Biol* 1:461-466; Lens et al. (2003) *EMBO J* 22:2934-2947)" (See Fig. 30,Table 2A, 2B, paragraph [1454], Girard et al.). It is noted that Lens et al. (2003) *EMBO J* 22:2934-2947, cited by Girard et al., teach mouse survivin and the phenotype of the survivin-deficient mice partially overlaps with that observed in mouse embryos deficient for INCENP.

With regard to polynucleotide encodes an immunoactive gene product, chemokine CCL21 (claims 1-2 and 51-53 of instant application), Girard et al. teach that human SLC/CCL21 cDNA encodes a 134 amino acid residue, highly basic, precursor protein with a 23 amino acid residue signal peptide that is cleaved to form the predicted 111 amino acid residues mature protein. Mouse SLC/CCL21 cDNA encodes a 133 amino acid residue protein with 23-residue signal peptide that is cleaved to generate the 110 residue mature protein. Human and mouse SLC/CCL21 is highly conserved, exhibiting 86% amino acid sequence identity (See paragraph [0014]).

With regard to immune response (claims 1-2, 26, 28 and 51-53 of instant application), Girard et al. teach "some chemokines act selectively on immune system cells such as subsets of T-cells or B lymphocytes or antigen presenting cells, and may thereby promote immune responses to antigens" (See paragraph [0012]).

With regard to vaccine and pharmaceutical composition, Girard et al. teach "some embodiments of the present invention relate to a device for delivering the THAP-type chemokine-binding agent or pharmaceutical composition thereof to the subject. In such embodiment, the device comprises a container that contains the THAP-type chemokine-binding agent or pharmaceutical composition thereof. For example, in some embodiments, the device may be a conventional device including, but not limited to, syringes, devices for intranasal administration of compositions and vaccine guns (See paragraph [1247]).

With regard to DNA construct for expression of proteins, Girard et al teach plasmids and other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses,

adenoviruses and adeno-associated viruses), which serve equivalent functions (See paragraph [0986]).

However, Girard et al. do not directly teach SEQ ID NO: 7, which encodes a murine CCL21.

At the time the claimed invention was made, SEQ ID NO: 7, which encodes a murine CCL21 is known in the art. For instance, Bennett et al. teach DNA encoding mouse CCL21 that matches perfectly with SEQ ID NO: 7 (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, detailed alignment of sequences listed below).

```
RESULT 1
AF006637
LOCUS       AF006637                615 bp    mRNA    linear   ROD 22-JUN-
1997
DEFINITION  Mus musculus beta-chemokine TCA4 mRNA, complete cds.
ACCESSION   AF006637
VERSION     AF006637.1  GI:2209188
KEYWORDS    .
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia;
            Sciurognathi; Muroidea; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 615)
  AUTHORS   Tanabe,S., Lu,Z., Luo,Y., Quackenbush,E.J., Berman,M.A.,
            Collins-Racie,L.A., Mi,S., Reilly,C., Lo,D., Jacobs,K.A. and
            Dorf,M.E.
  TITLE     Direct Submission
  JOURNAL   Submitted (03-JUN-1997) Genetics Institute, 87 Cambridge Park
            Drive, Cambridge, MA 02140, USA
FEATURES             Location/Qualifiers
     source          1. .615
                     /organism="Mus musculus"
                     /mol_type="mRNA"
                     /db_xref="taxon:10090"
                     /tissue_type="thymus"
                     /dev_stage="adult"
     CDS             97. .498
                     /note="beta-chemokine"
                     /codon_start=1
                     /product="TCA4"
```

/protein_id="AAB61440.1"
/db_xref="GI:2209189"

/translation="MAQMMTLSLLSLVLALCIPWTQGSDGGGQDCCLKYSQKKIPYSI

VRGYRKQEPSLGCPIPAILFSPRKHSKPELCANPEEGWVQNLMRRLDQPPAPGKQSPG
CRKNRGTSKSGKKGKGSKGCKRTEQTQPSRG"

ORIGIN

Query Match 100.0%; Score 615; DB 6; Length 615;
Best Local Similarity 100.0%; Pred. No. 3e-193;
Matches 615; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 GAATTCGGCCAAAGAGGCCTACGGCCAAAGAGGGCTAAACTTGCGGCTGTCCATCTCACC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GAATTCGGCCAAAGAGGCCTACGGCCAAAGAGGGCTAAACTTGCGGCTGTCCATCTCACC 60

Qy         61 TACAGCTCTGGTCTCATCCTCAACTCAACCACAATCATGGCTCAGATGATGACTCTGAGC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TACAGCTCTGGTCTCATCCTCAACTCAACCACAATCATGGCTCAGATGATGACTCTGAGC 120

Qy        121 CTCCTTAGCCTGGTCCTGGCTCTCTGCATCCCCTGGACCCAAGGCAGTGATGGAGGGGGT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 CTCCTTAGCCTGGTCCTGGCTCTCTGCATCCCCTGGACCCAAGGCAGTGATGGAGGGGGT 180

Qy        181 CAGGACTGCTGCCTTAAGTACAGCCAGAAGAAAATTCCCTACAGTATTGTCCGAGGCTAT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 CAGGACTGCTGCCTTAAGTACAGCCAGAAGAAAATTCCCTACAGTATTGTCCGAGGCTAT 240

Qy        241 AGGAAGCAAGAACCAAGTTTAGGCTGTCCCATCCCGGCAATCCTGTTCTCACCCCGGAAG 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 AGGAAGCAAGAACCAAGTTTAGGCTGTCCCATCCCGGCAATCCTGTTCTCACCCCGGAAG 300

Qy        301 CACTCTAAGCCTGAGCTATGTGCAAACCCTGAGGAAGGCTGGGTGCAGAACCTGATGCGC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 CACTCTAAGCCTGAGCTATGTGCAAACCCTGAGGAAGGCTGGGTGCAGAACCTGATGCGC 360

Qy        361 CGCCTGGACCAGCCTCCAGCCCCAGGGAAACAAAGCCCCGGCTGCAGGAAGAACCGGGGA 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 CGCCTGGACCAGCCTCCAGCCCCAGGGAAACAAAGCCCCGGCTGCAGGAAGAACCGGGGA 420

Qy        421 ACCTCTAAGTCTGGAAAGAAAGGAAAGGGCTCCAAGGGCTGCAAGAGAACTGAACAGACA 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 ACCTCTAAGTCTGGAAAGAAAGGAAAGGGCTCCAAGGGCTGCAAGAGAACTGAACAGACA 480

Qy        481 CAGCCCTCAAGAGGATAGCCCAGTAGCCCGCCTGGAGCCCAGGAGATCCCCCACGAACTT 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 CAGCCCTCAAGAGGATAGCCCAGTAGCCCGCCTGGAGCCCAGGAGATCCCCCACGAACTT 540

Qy        541 CAAGCTGGGTGGTTCACGGTCCAACTCACAGGCAAAGAGGGAGCTAGAAAACAGACTCAG 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 CAAGCTGGGTGGTTCACGGTCCAACTCACAGGCAAAGAGGGAGCTAGAAAACAGACTCAG 600
```

```
Qy        601 GAGCCGCTAGTCGAG 615
              |||||||||||||||
Db        601 GAGCCGCTAGTCGAG 615
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Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to modify the delivery of DNA construct by substituting human CCL21 taught by Girard et al. with murine CCL21 encoded by SEQ ID NO: 7, by the teachings of Tanabe et al., in order to analyze the capacities of different mammalian CCL21 in eliciting immune responses against cancer cells.

One having ordinary skill in the art would have been motivated to replace human CCL21 with murine CCL21 because with regard to analyses on eliciting immune responses against cancer cells by antigens, the murine animals are more accessible and can be easily manipulated for designed experimentations than humans.

There would have been a reasonable expectation of success given (i) human chemokine CCL21 murine chemokine CCL21 are homologues involved in regulation in immune responses by the teachings of Girard et al., and (ii) the exact polynucleotide sequences encoding murine CCL21, by the teachings of Tanabe et al. for a skilled person in the art to deliver a DNA construct expressing murine CCL21 as an antigen (that is, a DNA vaccine), to elicit an immune response against cancer cells in an murine animals.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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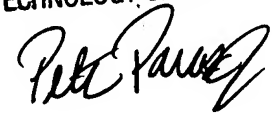
TECHNOLOGY CENTER 1600



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